SUBSTITUTE FORM PTO-1449 (MODIFIED) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	Attorney Docket No.	04844/005005
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(37 CFR §1.98(b))	IDS Filed	August 16, 2001
		21559

	OTHER DOCUMENTS (INCLUDING AUTHOR, TITLE, DATE, PLACE OF PUBLICATION)
CM	Kunugi et al., "C677T polymorphism in methylenetetrahydrofolate reductase gene and psychoses," *Mol. Psychiatr.* 3:435-437 (1998).
	Lanoue et al., "Antisense Inhibition of Methylenetetrahydrofolate Reductase Results in Neural Tube Defects in Cultured Mouse Embryos," *Experimental Biology Abstract* (1997).
	Matthews et al., "Methylenetetrahydrofolate reductase and methionine synthase: biochemistry and molecular biology," *Eur. J. Pediatr.* 157:S54-S59 (1998).
	Matthews, "Methylentetrahydrofolate reductase from pig liver," *Methods in Enzymology Vitamines and Coenzymes Part G* 122: 372-381 (1986).
	Molimard et al., "Does use of withdrawal of long-acting β_2-adrenoceptor induce desensitisation?," *Lancet* 351: 66-67 (1998).
	Morita et al., "Genetic polymorphism of 5,10 methylenetetrahydrofolate reductase (MTHFR) as a risk factor for coronary artery disease," *Circulation* 95:2032-2036 (1997).
	Mudd et al., "$N^{5,10}$-Methylenetetrahydrofolate reductase deficiency and schizophrenia: a working hypothesis," *J. Psychiat. Res. 11: 259-262 (1974).*
	Niefind et al., "Amino acid similarity coefficients for protein modeling and sequence alignment derived from main-chain folding angles," *J. Mol. Biol.* 219:481-497 (1991).
	Nurnberger et al., "Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative," *Arch. Gen. Psychiatry* 51:849-859, discussion 863-864 (1994).
	Orita et al., "Rapid and Sensitive Detection of Point Mutations and DNA Polymorphisms Using the Polymerase Chain Reaction," *Genomics* 5:574-579 (1989).
	Pasquier et al., "Methylenetetrahydrofolate reductase deficiency revealed by a neuropathy in a psychotic adult [letter]," *Journal of Neurology, Neurosurgery & Psychiatry* 57:765-766 (1994).
	Poirer et al., "Apolipoprotein E4 allele as a predictor of cholinergic deficits and treatment outcome in Alzheimer disease," *Proc. Natl. Acad. Sci. USA* 92:12260-12264 (1995).
	Refsum et al., "Homocysteine and vascular disease," *Annu. Rev. Medicine* 48:31-62 (1998).
	Regland et al., "Homocysteinemia and schizophrenia as a case of methylation deficiency," *Journal of Neural Transmission-General Section* 98:143-152 (1994).
	Regland et al., "Homocysteinemia is a common feature of schizophrenia," *Journal of Neural Transmission-General Section* 100:165-169 (1995).
	Regland et al., "Homozygous thermolabile methylenetetrahydrofolate reductase in schizophrenia-like psychosis," *Journal of Neural Transmission 104:931-941 (1997).*
	Rozen, "Molecular genetics of methylenetetrahydrofolate reductase deficiency," *J. Inher. Metab. Dis.* 19:589-594 (1996).

EXAMINER	DATE CONSIDERED
Carlo Myers	3-~~30~~ 12-03

EXAMINER: Initial citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with the next communication to applicant.

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U.S. PATENTS

Examiner's Initials	Patent Number	Issue Date	Patentee	Class	Subclass	Filing Date (If Appropriate)
CM	5,972,614	10/26/99	Ruano et al.	435	6	
CM	6,008,221	12/28/99	Smith et al.	514	254	

FOREIGN PATENT OR PUBLISHED FOREIGN PATENT APPLICATION

Examiner's Initials	Document Number	Publication Date	Country or Patent Office	Class	Subclass	Translation (Yes/No)
CM	WO 00/04194	27.01.00	PCT			
CM	WO 95/33054	7.12.95	PCT			

OTHER DOCUMENTS (INCLUDING AUTHOR, TITLE, DATE, PLACE OF PUBLICATION)

CM	Akar et al., "Effect of methylenetetrahydrofolate reductase 677 C-T, 1298 A-C, and 1317 T-C on factor V 1691 mutation in Turkish deep vein thrombosis patients," *Thromb. Res.* 97:163-167(2000).
	Araki et al., "Determination of free and total homocysteine in human plasma by high-performance liquid chromatography with fluorecence detection," *J. Chromatography* 422:43-52 (1987).
✓	Arinami et al., "Methylenetetrahydrofolate Reductase Variant and Schizophrenia/Depression," *Amer. J. of Medical Genetics* 74:526-528 (1997).
	Arranz et al., "Evidence for association between polymorphisms in the promoter and coding regions of the 5-HT_{2A} receptor gene and response to clozapine," *Molecular Psychiatry* 3:61-66 (1998).
	Bakker et al., "Hyperhomocysteinaemia and associated disease," *Pharm. World Sci.* 19:126-132 (1997).
	Boushey et al., "A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. Probable benefits of increasing folic acid intakes," *JAMA* 274:1049-1057 (1995).
	Brattstrom et al., "Plasma homocysteine and methionine tolerance in early-onset vascular disease," *Homeostasis* 19:35-44 (1989).
	Breier et al., "National Institute of Mental Health longitudinal study of chronic schizophrenia. Prognosis and predictors of outcome," *Arch. Gen. Psychiatry* 48:239-246 (1991).
✓	Chapman et al., "ACE, MTHFR, Factor V Leiden, And APOE Polymorphisms In Patients With Vascular And Alzheimer's Dementia," *Stroke* 29:1401-1404 (1998).
	Christensen et al., "Correlation of a Common Mutation in the Methylenetetrahydrofolate Reductase Gene With Plasma Homocysteine in Patients With Premature Coronary Artery Disease," *Arteriosclerosis, Thrombosis, and Vascular Biology* 17:569-573 (1997).
	Christensen et al., "Genetic polymorphisms in methylenetetrahydrofolate reductase and methionine synthase, folate levels in red blood cells, and risk of neural tube defects," *Am. J. Med. Genet.* 84:151-157 (1999).

EXAMINER Carla Myers	DATE CONSIDERED 3-12-03

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U.S. PATENTS	
OTHER DOCUMENTS (INCLUDING AUTHOR, TITLE, DATE, PLACE OF PUBLICATION)	
CM	Clarke et al., "Hyperhomocysteinemia: an independent risk factor for vascular disease," *N. Engl. J. Med.* 324:1149-1155 (1991).
	Cormack, "Directed mutagenesis using the polymerase chain reaction," *Current Protocols in Molecular Biology* 1:8.5.1-8.5.9, John Wiley & Sons, New York (1995).
	Dalman et al., "Obstetric complications and the risk of schizophrenia; a longitudinal study of a national birth cohort," *Arch. Gen. Psychiatry* 56:234-240 (1999).
	Drazen et al., " Treatment of Asthma with Drugs Modifying the Leukotriene Pathway," *N.E. Journal of Medicine* 340:197-206 (1999).
	Drazen et al., "Pharmacogenetic association between ALOX5 promoter genotype and the response to anti-asthma treatment," *Nature Genetics* 22:168-170 (1999).
	Endicott et al., "The global assessment scale, a procedure for measuring overall severity of psychiatric disturbance," *Arch. Gen. Psychiatry* 33:766-771 (1976).
	Engbersen et al., "Thermolabile 5, 10-Methylenetetrahydrofolate Reductase as a Cause of Mild Hyperhomocysteinemia," *Am. J. Hum. Genet.* 56:142-150 (1995).
	Fletcher et al., "MTHFR association with arteriosclerotic vascular disease," *Human Genet.* 103:11-21 (1998).
	Freeman et al., "Folate-Responsive Homocystinuria and Schizophrenia. A defect in Methylation Due to Deficient 5, 10-Methylenetetrahydrofolate Reductase Activity," *N.E. Journal of Medicine* 292:491-496 (1975).
	Frosst et al., "A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase," *Nature Genetics* 10:111-113 (1995).
	Gallagher et al., "Homocysteine and risk of premature coronary heart disease. Evidence for a common gene mutation," *Circulation* 94:2154-2158 (1996).
	Goyette et al., "Gene structure of human and mouse methylenetetrahydrofolate reductase (MTHFR)," *Mammalian Genome* 9:652-656 (1998).
	Goyette et al., "Human methylenetetrahydrofolate reductase: isolation of cDNA, mapping and mutation identification," *Nature Genetics* 7:195-200 (1994).
	Goyette et al., "Seven Novel Mutations in the Methylenetetrahydrofolate Reductase Gene and Genotype/Phenotype Correlations in Severe Methylenetetrahydrofolate Reductase Deficiency," *Am. J. Hum. Genet.* 56:1052-1059 (1995).
	Goyette et al., "Severe and mild mutations in *cis* for the methylenetetrahydrofolate reductase (MTHFR) gene, and description of five novel mutations in MTHFR," *Am. J. Hum. Genet.* 59:1268-1275 (1996).
	Grandone et al., "Factor V Leiden, C>T MTHFR polymorphism and genetic susceptibility to preeclampsia," *Thromb. Haemost.* 77:1052-1054 (1997).

EXAMINER Carla Myers	DATE CONSIDERED 3-12-03

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U.S. PATENTS

	OTHER DOCUMENTS (INCLUDING AUTHOR, TITLE, DATE, PLACE OF PUBLICATION)
CM	Grandone et al., "Methylenetetrahydrofolate reductase (MTHFR) 677-->C mutation and unexplained early pregnancy loss [letter]," *Thrombosis & Haemostasis* 79:1056-1057 (1998).
	Grieco, "Homocystinuria: pathogenetic mechanisms," *Am. J. Med. Sci.* 273:120-132 (1977).
	Gudnason et al., "C677T (thermolabile alanine/valine) polymorphism in methylenetetrahydrofolate reductase (MTHFR): its frequency and impact on plasma homocysteine concentration in different European populations." *Atherosclerosis* 136:347-354 (1998).
	Guenther et al., "The structure and properties of methylenetetrahydrofolate reductase from *Escherichia coli*: a model for the role of folate in ameliorating hyperhomocysteinemia in humans," *Nature Struct. Biol.* 6:359-365 (1999).
	Haagsma et al., "Influence of sulphasalazine, methotrexate, and the combination of both on plasma homocysteine concentrations in patients with rheumatoid arthritis," *Ann. Rheum. Dis.* 58:79-84 (1999).
	Haworth et al., "Symptomatic and asymptomatic methylenetetrahydrofolate reductase deficiency in two adult brothers," *Am. J. of Medical Genetics* 45:572-576 (1993).
	Higgins et al., "NHLBI Family Heart Study: Objectives and Design," *Am. J. Epidemiol.* 143:1219-1228 (1996).
	Hol et al., "Molecular genetic analysis of the gene encoding the trifunctional enzyme MTHFD (methylenetetrahydrofolate-dehydrogenase, methylenetetrahydrofolate-cyclohydrolase, formyltetrahydrofolate synthetase) in patients with neural tube defects," *Clin. Genet.* 53:119-125 (1998).
	Jacques et al., "Relation Between Folate Status, a Common Mutation in Methylenetetrahydrofolate Reductase, and Plasma Homocysteine Concentrations," *Circulation* 93:7-9 (1996).
	James et al., "Abnormal folate metabolism and mutation in the methylenetetrahydrofolate reductase gene may be maternal risk factors for Down syndrome," *Am. J. Clin. Nutr.* 70:495-501 (1999).
	Joober et al., "Polyglutamine-containing proteins in schizophrenia," *Mol. Psychiatry* 4:53-57 (1999).
	Kane et al., "Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine," *Arch. Gen. Psychiatry* 45:789-796 (1988).
	Kang et al., "Thermolabile methylenetetrahydrofolate reductase: An inherited risk factor for coronary artery disease," *Am. J. Human Genet.* 48:536-545 (1991).
	Kluijtmans et al., "Molecular genetic analysis in mild hyperhomocysteinemia: A common mutation in methylenetetrahydrofolate reductase gene is a risk factor for cardiovascular disease," *Am. J. Hum. Genet.* 58:35-41 (1996).
	Koreen et al., "Plasma homovanillic acid levels in first-episode schizophrenia. Psychopathology and treatment response," *Arch Gen. Psychiatry* 51:132-138 (1994).
	Kuivenhoven et al., "The Role of a Common Variant of the Cholesteryl Esterr Transfer Protein Gene in the Progression of Coronary Atherosclerosis," *N.E. Journal of Medicine* 338:86-93 (1998).

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CM	Saint-Girons et al., "Nucleotide sequence of metF, the E.coli structural gene for 5-10 methylene tetrahydrofolate reductase and of its control region," *Nucleic Acids Research* 11:6723-6732 (1983).
	Schwartz et al., "Myocardial Infarction In Young Women In Relation To Plasma Total Homocysteine, Folate, And A Common Variant In The Methylenetetrahydrofolate Reductase Gene," *Circulation* 96(2):412-417 (1997).
	Selhub et al., "Association between plasma homocysteine concentrations and extra-cranial carotid artery stenosis," *N. Engl. J. Med.* 332:286-291 (1995).
	Shin-Buehring et al., "A new enzymatic method for pyridoxal-5-phosphate determination," *J. Inherit. Metab. Disorders* 4:123-124 (1981).
	Skibola et al., "Polymorphisms in the methylenetetrahydrofolate reductase gene are associated with susceptibility to acute leukemia in adults," *Proc. Natl. Acad. Sci. USA* 96:12810-12815 (1999).
	Smeraldi et al., "Polymorphism within the promoter of the serotonin transporter gene and antidepressant efficacy of fluvoxamine," *Molecular Psychiatry* 3:508-511 (1998).
	Sohda et al., "Methylenetetrahydrofolate reductase polymorphism and pre-eclampsia," *J. Med. Genet.* 34: 525-526 (1997).
	Spire-Vayron de la Moureyre et al., "Genotypic and phenotypic analysis of the polymorphic thiopurine S-methyltransferase gene (TPMT) in a European population," *British Journal of Pharmacology* 125:879-887 (1998).
	Stauffer et al., "Cloning and nucleotide sequence of the *Salmonella typhimurium* LT2 *metF* gene and its homology with the corresponding sequence of *Escherichia coli*," *Mol. Gen. Genet.* 212:246-251 (1988).
	Szymanski et al., "Gender differences in onset of illness, treatment response, course, and biologic indexes in first-episode schizophrenic patients," *Am. J. Psychiatry* 152:698-703 (1995).
	Tan et al., "Association between β_2-adrenoceptor polymorphism and susceptibility to bronchodilator desensitisation in moderately severe stable asthmatics," *Lancet* 350:995-999 (1997).
	Tan et al., "Does use of withdrawal of long-acting β_2-adrenoceptor induce desensitisation?," *Lancet* 351:995-999 (1997).
	Third Wave Technologies, "Third Wave Technologies Launches Third Pharmacogenetic Product. Oligonucleotide Sets and Assay Controls Specific for MTHFR Mutation," *News release* December (1999).
	Tsuang et al., "Heterogeneity of schizophrenia. Conceptual models and analytic strategies," *Br. J. Psychiatry* 156:17-26 (1990).
	Ueda et al., "ACE (I/D) Genotype as a Predictor of the Magnitude and Duration of the Response to an ACE Inhibitor Drug (Enalaprilat) in Humans," *Circulation* 98:2148-2153 (1998).
	van der Put et al., "A Second Common Mutation in the Methylenetetrahydrofolate Reductase Gene: An Additional Risk Factor for Neural-Tube Defects?," *Am. J. Hum. Genet.* 62:1044-1051 (1998).

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CM	van der Put et al., "Mutated methylenetetrahydrofolate reductase as a risk factor for spina bifida," *Lancet* 346:1070-1071 (1995).
	van Ede et al., "Methotrexate in Rheumatoid Arthritis: An Update with Focus on Mechanisms Involved in Toxicity", *Seminar In Arthritis and Rheumatism,* 27:277-292 (1998).
	Viel et al., "Loss of Heterozygosity at the 5, 10- Methylenetetrahydrofalate Reductase locus in Human Ovarian Carcinomas", *British Journal of Cancer* 75:1105-1110 (1997) .
	Weisberg et al., "A second Genetic Polymorphism in Methylenetetrahydrofolate Reductase (MTHFR) Associated with Decreased Enzyme Activity," *Molecular Genetics and Metabolism* 64:169-172 (1998).
	Whitehead et al., "A genetic defect in 5, 10 methylenetetrahydrofolate reductase in neural tube defects," *Q J Med.* 88:763-766 (1995).
	Woerner et al., "Anchoring the BPRS: an aid to improved reliability," *Psychopharmacol. Bull.* 24:112-117 (1988).
	Wyatt, "Neuroleptics and the natural course of schizophrenia," *Schizophr. Bull.* 17:325-351 (1991).
	Yang et al., "Molecular cloning and nucleotide sequence analysis of the *Saccharomyces cerevisiae RAD1* gene," *Mol. Cell. Biol.* 4:2161-2169 (1984).
CM	Zhou et al., "Purification and Characterization of Methylenetetrahydrofolate Reductase from Human Cadaver Liver," *Biochemical Medicine and Metabolic biology* 43:234-242 (1990).

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